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Mortality and morbidity among pregnant women with COVID-19 infection: a meta-analysis

Aida Musyarrofah[1], Anung Putri Illahika[2], Probo Yudha Pratama Putra[3], Dinda Amalia Eka Putri[3], S. Khansa Zatalini[3], Yohanes Eddy Prasetyo[3]
[1]Department of Obstetric and Gynecology, Faculty of Medicine, University of Muhammadiyah Malang, Malang, Indonesia
[2]Department of Anatomy, Faculty of Medicine, University of Muhammadiyah Malang, Malang, Indonesia
[3]Faculty of Medicine, University of Muhammadiyah Malang, Malang, Indonesia

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ABSTRACT

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and declared as a global pandemic in March 2020. There is a special immune tolerance in pregnant woman, predisposes to a viral infection, then increased risk severe complication. Meta analysis was performed using preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidlines with comprehensive literature study was performed in July 2021 through Science Direct, Cochrane, and PubMed, with keywords "COVID-19", "SARS-CoV-2", "pregnancy", "pregnant", and "complication", and each parameter we assessed using review manager 5.3. Nine studies with 30,257 infected patients and 1,678,974 non infected patients were included. The data show that preterm birth (odds ratio (OR)=1.43, 95% confidence interval (CI): 1.17-1.74; p=0.0004, inconsistency (I2) =90%) less in non infected groups, no camparable finding in vaginal delivery (OR=0.93, 95% CI: 0.82-1.06; p<0.030, I2=75%) and caesarian delivery (OR=1.07, 95% CI: 0.90-1.28; p<0.045, I2=96%). Intensive care unit (ICU) admission reported high percentage in infected patients (OR=4.87, 95% CI: 3.08-7.71; p<0.0001, I2=93%), we found that obstetric complication in subgroup (OR=1.31, 95% CI: 0.13-1.52; p<0.0003, I2=54%) and mortality (OR=17.41, 95% CI: 11.04-27.46; p<0.0001, I2=0%) less in non infected patients. Pregnancy with infected COVID-19 has high percentage of mortality and morbidity events. Infected and non infected patient has equal chance for vaginal or caesarian delivery.

Corresponding Author:

Anung Putri Illahika
Department of Anatomy, Faculty of Medicine, University of Muhammadiyah Malang
Bendungan Sutami Street No.188, Sumbersari, Lowokwaru, Malang, Indonesia
Email: anungputri113@gmail.com

1. INTRODUCTION

The severe acute respiratory condition caused by coronavirus disease 2019 (COVID-19) was proclaimed a global pandemic in March 2020 [1]. The virus has infected over 27 million people and caused over 880,000 deaths worldwide [2]. Approximately 31.5% of pregnant women reported receiving treatment, but only 5.8% of these data were reported to the centers for disease control and prevention (CDC) by non-pregnant women [3].

Coronavirus is a virus that has an envelope, does not fragment, and consists of a single ribonucleotide nucleic acid (RNA), which can cause serious fetal illness [4]. Due to the physiological

changes of the immunological and cardiopulmonary systems that occur during pregnancy, pregnant women may suffer more severe symptoms after a viral respiratory infection. [5]. We performed a systematic review and meta-analysis on pregnant COVID-19 patients. It aims to evaluate the association between severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and maternal outcomes challenges clinical practice to provide recommendations based on data for the treatment of pregnant and recently pregnant women with COVID-19.

2. RESEARCH METHOD

2.1. Literature search

The meta-analysis was conducted using the preferred reporting items for systematic reviews and meta-analyses (PRISMA) principles as depicted in Figure 1 [6]. A complete search was conducted on PubMed, science direct, and cochrane library. The following keywords were included in the search: i) complication; ii) COVID-19; iii) SARS-CoV-2; iv) pregnancy; v) pregnant; and vi) pregnancy.

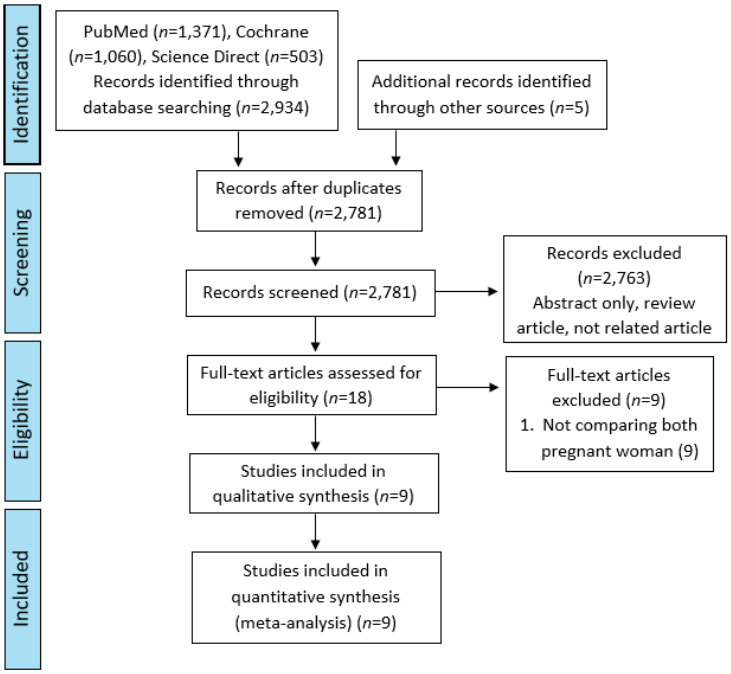

Figure 1. Article screening using PRISMA flow chart

2.2. Eligibility criteria

The following are the requirements for inclusion: i) Pregnant women infected with COVID 19; ii) a comparison of the outcomes of infected and uninfected pregnant women; iii) studies having data that may be analyzed; and iv) cohort studies. While exclusion criteria include: i) non-pregnant women; ii) Not comparing infected and non-infected pregnant women; and iii) Case series, review, or systematic review studies.

2.3. Outcome assessed

Preterm birth, vaginal delivery, caesarian delivery, intensive care unit (ICU) admission, premature rupture of membaranes (PROM), pre-eclampsia, placental abruption, chorioamnionitis, intrauterine fetal death (IUFD), postpartum hemorrhage (PPH), and mortality were evaluated.

2.4. Assesment study quality

We utilized the New Castle-Ottawa scale with a range of 0-9 to evaluate the quality of the non-randomized study [7]. A study with a score of 7-9 has great quality, 4-6 has a significant risk of bias, and 0-3 has a very high risk of bias. Each study's level of evidence was assessed using the available criteria of the Oxford center for evidence-based medicine [8].

2.5. Statistical analysis

Statistical analysis was performed with review manager version 5.3. For each parameter, the combined odds ratio (OR) and 95 percent confidence interval (CI) were estimated, and mean differences (MD) were computed. In addition, the cochrane chi-squared test and inconsistency (I2) were employed to assess the heterogeneity of the studies. When I2 was greater than 50%, it was important.

3. RESULTS AND DISCUSSION

3.1. Baseline characteristic feature

The primary database was searched for a total of 30,257 articles, and five additional studies were collected via references. In the end, we included nine publications covering a total of 1,678,974 eligible patients. Table 1 demonstrates the characteristics of the listed studies. The determination level of the evidence base was 2b for nine cohort studies, and all included studies were of excellent quality according to the New Castle–Ottawa scale, which ranges from 7 to 9.

Table 1. Characteristic of study and study quality

Reference	Country	Study design	LE	New Ottwa Scale	CASES (n)	
					Infected	Not infected
Adhikari 2020 [9]	USA	Cohort	2b	8	245	3,035
Chinn 2021 [10]	USA	Cohort	2b	7	18,715	850,364
Hcini 2021 [11]	French Guiana	Cohort	2b	8	137	370
Ko 2021 [12]	USA	Cohort	2b	7	6,550	482,921
Mrtinez-Perez 2021 [13]	Spain	Cohort	2b	8	246	763
Prabhu 2020 [14]	USA	Cohort	2b	8	70	605
Steffen 2021 [15]	USA	Cohort	2b	8	61	939
Urganci 2021 [16]	U.K	Cohort	2b	7	3,527	338,553
Villar 2021 [17]	U.K	Cohort	2b	8	706	1,424

(LE: level of evidence base; 2b: level of evidence cohort study)

3.2. Maternal and obstetric outcome

3.2.1. Preterm birth

The statistical difference between the two groups of 29,777 infected patients and 1,662,915 non-infected patients is depicted in Figure 2 by nine studies that were combined for analysis. It indicated that mothers infected with COVID 19 are more likely to give birth prematurely (OR=1.43, 95% CI: 1.17-1.74; p=0.0004). Concerning heterogeneity, the chi-square test revealed a high level of heterogeneity (I2= 90%). COVID-19 infects individuals through the angiotensin-converting enzyme-II receptor (ACE-II), which is abundant in alveolar epithelium and cells between the maternal-fetal junction [18]. The presence of ACE-II in the reproductive tract and placenta may influence the outcome of a pregnancy [19]. This may be due to the activation of pro-inflammatory cytokines by COVID-19 infection, which can lead to placental mal-perfusion and reduced placental function, both of which can lead to preterm birth [20], [21]. A forest plot presents meta-analysis effect estimates and confidence intervals. Each study is represented by a block at the intervention impact point estimate, with horizontal lines extending on either side of the block.

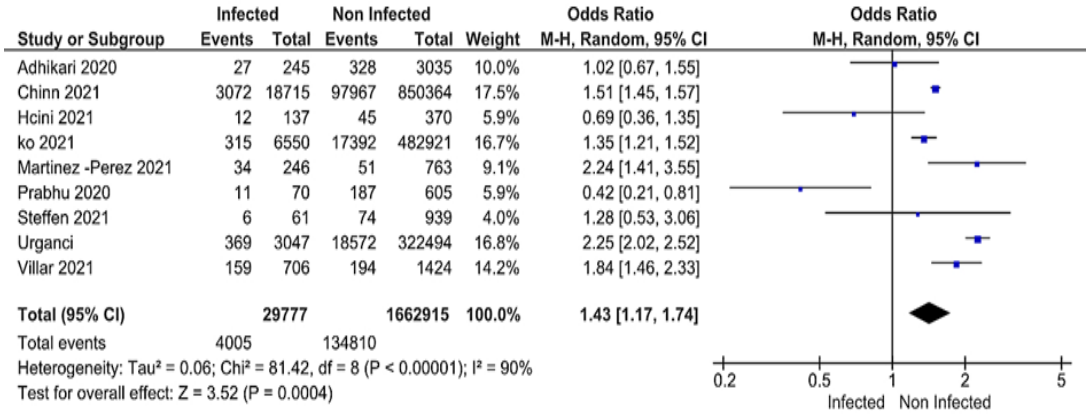

Figure 2. Forest plot preterm birth

3.2.2. Delivery mode

Seven studies found no statistically significant changes in vaginal delivery outcomes between infected and uninfected individuals in Figure 3 (OR=0.93, 95% CI: 0.82-1.06; p=0.030) and revealed a high degree of heterogeneity between the two groups (I2=75). Figure 4 displays the caesarean delivery results for 30,257 infected patients and 1,678,978 non-infected patients with no statistically significant differences (OR=1.07, 95% CI: 0.90-1.20; p=0.045) and a large heterogeneity (I2=96%) between the two groups. Individualized delivery should be used base on disease severity and the obstetric indications. Delivery route showed no difference between caesarian and vaginal delivery, and the rate of neonatal and maternal mortality of COVID-19 was not higher when the mother gave birth vaginally [22]–[25].

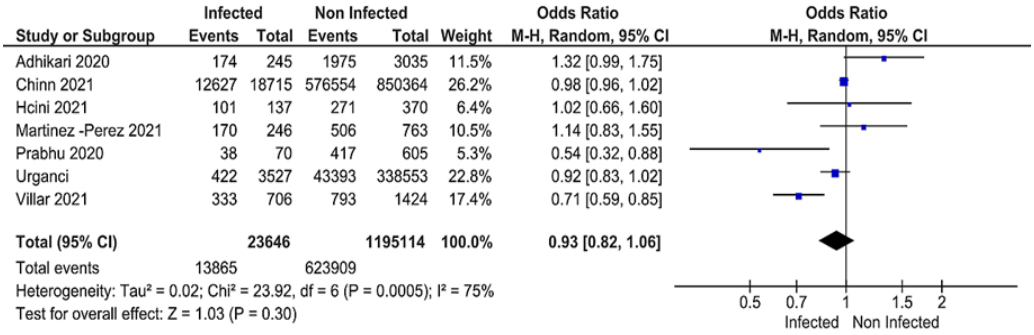

Figure 3. Forest plot vaginal delivery

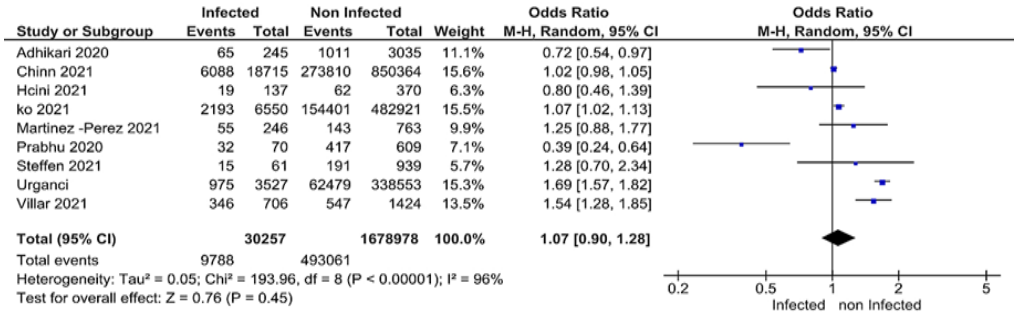

Figure 4. Forest plot caesarian delivery

3.2.3. ICU admission

Seven studies revealed statistically significant differences in ICU admission rates between infected and non-infected patients as shown in Figure 5. Non-infected groups reported fewer ICU admissions (OR=4.87, 95% CI: 3.08-7.71; p=0.0001), with considerable heterogeneity between the two groups (I2=93%). Infected pregnant women have a high rate of ICU admission. Ellington *et al*. highlight in their study that maternal mortality, ICU admission, and mechanical ventilation are on the rise [3].

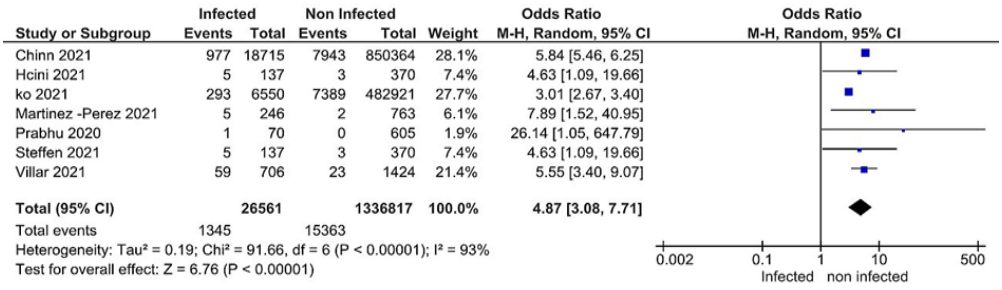

Figure 5. Forest plot ICU admission

In pregnant women, the reported admission rate can increase with age, from 0% in women aged 25 to 29 years to 33% in those aged 40 to 49 years, and increasing oxygen demand and physiologic anemia can exacerbate the severity of the illness [26], [27]. On the other hand, infected coronavirus disease 2019 during pregnancy is also associated with an increased risk of adverse maternal and neonatal outcomes [28]. 5% of hospitalized pregnant women with COVID-19 required ICU admission, and less than 1% required extracorporeal membrane oxygenation, according to the UK obstetric surveillance system [29], [30].

3.2.4. Complication

We reported complications in the subgroup depicted in Figure 6, and three studies found no significant difference in the incidence of abruption between the two groups (OR=1.13; 95% CI:0.69-6.69; p=0.89). Chorioamnionitis did not differ significantly between two investigations (OR=0.86, 95% CI: 0.57-1.31; p=0.48). PROM (OR=1.15, 95% CI: 0.73-1.80; p=0.55), IUFD (OR=2.24, 95% CI: 0.76-6.62; p=0.14) and PPH (OR=1.33, 95% CI: 0.90-1.98; p=0.16) indicated no statistical difference between the two groups; however, pre-eclampsia was observed less frequently in non-infected individuals (OR=1.42, 95% CI: 1.21-1.68; p=0.0001) Non-infected patients reported fewer complications (OR=1.31; 95% CI: 0.13-1.52; p=0.0003), with moderate heterogeneity (I2=54%).

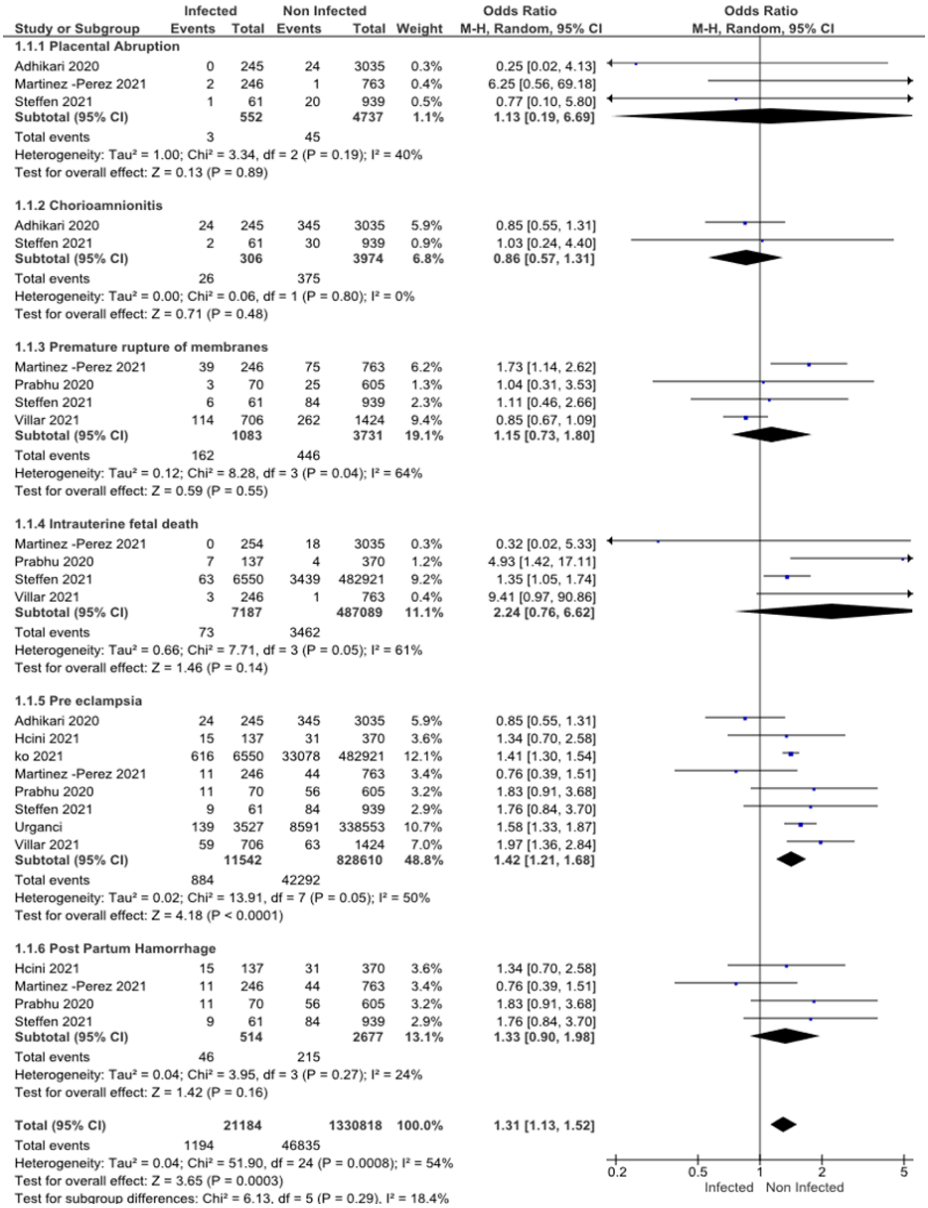

Figure 6. Forest plot complication

Given the high prevalence of problems in infected pregnant women in our investigations, it's possible that maternal and fetal immunological and trophoblast responses to COVID-19 may enhance maternal risks for obstetrical complications, as well as child risk for short- and long-term non-communicable diseases (NCD) [20]. Villar *et al*. discovered a strong correlation between pre-eclampsia and COVID 19. It's possible that maternal-fetal immune effectors and trophoblasts' pro-inflammatory immune responses to COVID-19 increase maternal risk of obstetrical problems and perhaps offspring risk of short- and long-term NCD. which is consistent with our findings [17]. The placentas of COVID-19-infected women show vascular changes that are similar to preeclampsia, but the condition of systemic inflammation and hypercoagulability like in non-pregnant people with severe illness and COVID-19 can be related to preeclampsia [31]–[33]. Our investigation observed no difference in the incidence of placental abruption and chorioamionitis; however, several studies found infiltration of intervillous macrophages (intervillosis) within the placenta [34]. COVID-19 may have contributed to the placental inflammation that led to vascular malperfusion, which finally led to preeclampsia and a deterioration of the mother's condition, such as abruption and Chorioamnionitis, [35]–[37]. PROM and IUFD are not significance difference in in our study, Taghavi et al reported no incidence PROM and IUFD in their study [38]. PPH was no significance difference in our studies, pregnant woman does not have increased risk in COVID-19 infection. Several studies from China found no difference in the incidence of postpartum hemorrhage in vaginal and cesarean according with risk of postpartum haemorrhage, when comparing the severity of COVID-19 [39]–[41].

3.2.5. Mortality

Three investigations demonstrated statistically significant differences in mortality between 25,971 infected individuals and 1,334,709 non-infected patients as shown in Figure 7. The death rate was high in infected groups (OR=17.41, 95% CI: 11.04-27.46; p=0.0001), and there was no heterogeneity between the two groups (I2=0%). Mortality was observed to be higher in infected pregnant women, which may occur even in the absence of significant baseline comorbidities. The acute respiratory distress syndrome (ARDS) and sepsis may be the leading causes of death [42]–[45]. Several causes, including viral and bacterial components, sepsis, superantigens, toxins, and antibodies, might trigger the unregulated release of cytokines [46]. Cardiac involvement has been documented in a number of cases with cormobidities and elevated troponin levels, resulting in mortality [47]–[49]. In severe cases, inflammation also increased the chance of multi-organ failure [50]. Our study is still far from knowing about morbidity and mortality, with very high heterogeneity further studies with a larger sample size are needed.

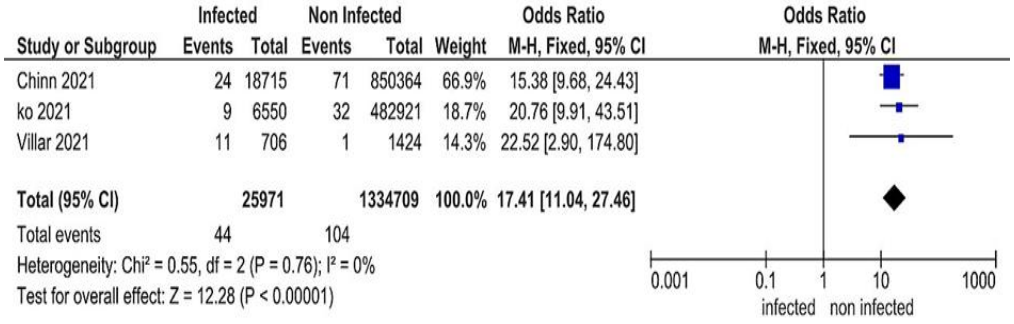

Figure 7. Forest plot mortality

4. CONCLUSSION

This study concluded that mortality and morbidity infected pregnant woman has a high rate than non pregnant woman. Both of group has equal chance for delivery route. Furthermore, the indication and delivery mode should be separated according to indication and maternal condition.

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BIOGRAPHIES OF AUTHORS

Aida Musyarrofah was born in Sumenep on 4th September 1982, she is a lecturer in medical faculty of University Muhammadiyah of Malang since 2018 until now. She work in Obstetric and Gynaecology Departement. She was completed study as obstetrician at Medical Faculty of Airlangga University. Aida have some article. The title article are Decreasing pain scale patients with endometriosis before and after laparoscopic conservative surgery followed with or without medical therapy. She can be contacted at email: adida.m@gmail.com.

Anung Putri Illahika was born in Surabaya on March 11, 1986. She is a lecturer in medical faculty of University Muhammadiyah of Malang since 2011 until now. She works in Anatomy Departement. She completed magister program of Anatomy-Histology at Medical Faculty of Airlangga University. She can be contacted at email: anungputri113@gmail.com.

Probo Yudha Pratama Putra was born in Jakarta on 3rd December 1990. He is an Instructure and research assistant in Obstetric and Gynecology Department medical faculty of University Muhammadiyah of Malang since 2017 until now. He also General practicioner in mother and child hospital Galeri Candra He completed Medical School at Medical Faculty of Muhammadiyah Malang University. He published an article in title Laparoscopic myomectomy versus open myomectomy in uterine fibroid treatment: A meta-analysis. He can be contacted at email: Probo@umm.ac.id.

Dinda Amalia Eka Putri was born in Gresik on 16th April 1994. She is an instructure and research assistant in Internal Medicine Department medical faculty of University Muhammadiyah of Malang. She completed Medical School at Medical Faculty of Muhammadiyah Malang University. She can be contacted at email: dndamalia@gmail.com.

S. Khansa Zatalini was born in Malang, 27th of August 1994. She is an Instructure and research Asistant at Medical Faculty University of Muhammadiyah Malang since 2019 until now. She completed her medical school in 2018, at University of Muhammadiyah Malang either. She can be contacted at email: kazatalini@umm.ac.id.

Yohanes Eddy Prasetyo was born on July 23, 1998 in Tulung Agung, East Java, Indonesia. He is a Clinical year student of the Medical Faculty from the University of Muhammadiyah Malang. He is very interested in research, apart from carrying out his profession, he is also a research assistant. He can be contacted at email: yohaneseddy@webmail.umm.ac.id.